Zinc: Does it Have Radioprotective Effect on Major Salivary Glands?

Çinko: Major Tükürük Bezlerine Radyoprotektif Etkisi Var Mıdır?

Zinc for Salivary Gland Radioprotection

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Özet

Amaç: Yüksek doz Radyoaktif iyot (131I) sonrası major tükürük bezlerinde çinkonun radyoprotektif etkisini histopatolojik inceleme ile değerlendirmektir.Gereç ve Yöntem: Onaltı Wistar albino rat her grupta sekiz hayvan olacak şekilde iki gruba ayrıldı. 131I grubunda (Grup 1) her bir rata 3 mCi 131I uygulandı. 131I ve çinko grubunda (Grup 2) çinko gastrik sonda ile 131I'den iki gün önce başlanıp 131I tedavisinden sonra beş gün devam edildi. Çinkonun son dozundan 24 saat sonra hayvanlar sakrifiye edilip, parotis, submandibular ve sublingual bezler histopatolojik inceleme için bilateral çıkarıldı. Kesitlerde asiner epitel hücrelerinde; ödem, vakuolizasyon, panasiner inflamasyon, nekroz ve atrofi, interstisyel alanda; periduktal fibrozis, periduktal infiltrasyon ve periduktal kaçak; duktal sistemde kanal ektazi ve skuamöz metaplazi ve vasküler sistemde skleroz ve darlık (fibrin trombüs) değerlendirildi. Bulgular: Ödem, vakuolizasyon, panasiner inflamasyon, nekroz, atrofi, periduktal fibrozis, periduktal inflamasyon, periduktal kaçak, duktal ektazi, skuamöz metaplazi, skleroz ve darlık submandibuler bezde periduktal inflamasyon dışında tüm bezlerde çinko grubunda daha az görülmüştür. Ancak bu veriler sublingual bezde atrofi dışında istatistiksel olarak anlamlı değildi. Submandibuler bezde çinko grubunda kontrol grubu ile karşılaştırıldığında önemli ölçüde daha az atrofi görüldü. Tartışma: Submandibuler bezde periduktal inflamasyon dışında her iki bez için tüm histopatolojik değişiklikler çinko grubunda daha düşük düzeyde idi. Bu bulgu çinko'nun erken dönem 131I hasarına karşı koruyucu bir etkisi olabileceğini gösterebilir.

Anahtar Kelimeler

Radyasyondan Koruma; Rat; Çinko; Tükürük Bezleri

Abstract

Aim: To evaluate the radioprotective effect of zinc on the major salivary glands with histopathological examination after high doses of radioiodine (131I). Material and Method: Sixteen Wistar albino rats were divided into two groups, eight animals in each group. Three mCi 131I was administrated to each rat in the 131I group (Group 1). Zinc was started via gastric gavage two days before 131I administration and was continued for five days after 131I therapy in the zinc group (Group 2). Twenty-four hours after the last dosage of zinc, the animals were sacrificed and the parotid, submandibular, and sublingual glands were removed bilaterally for histopathological examination. Oedema, vacuolization, panacinar inflammation, necrosis and atrophy in acinar epithelial cells; periductal fibrosis, periductal infiltration, and periductal leakage in interstitial space; duct ectasia and squamous metaplasia in the ductal system; and sclerosis and stenosis (fibrin thrombi) in the vascular system were evaluated in slices. Results: Levels of oedema, vacuolization, panacinar inflammation, necrosis, atrophy, periductal fibrosis, periductal inflammation, periductal leakage, ductal ectasia, squamous metaplasia, and sclerosis and stenosis were lower in the zinc group in all glands, except for the level of periductal inflammation in the submandibular gland. But these results were not statistically significant, except for atrophy in the sublingual gland. In the submandibular gland, atrophy was seen significantly less in the zinc group when compared with the control group. Discussion: All of the histopathological changes were at a lower level in the zinc group in all of the glands, except for periductal inflammation in the submandibular gland. This result may show the beneficial effect of zinc on early damage of 131I.

Keywords

Radiation Protection; Rats; Zinc; Salivary Glands

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Introduction

Radioiodine (131I) has been used for the treatment of hyperthyroidism and well differentiated thyroid carcinomas [1]. 131I is a radioisotope that emits beta and gamma rays, is administered orally, and is excreted via the renal system [2]. The usage of 131I therapy for hyperthyroidism, thyroid remnant ablation, and thyroid metastases is based on the radiation-induced cell damage caused by the beta radiation [3]. High doses of emitted ionizing radiation cause cell death, mainly through free radical formation [4].

The sodium/iodide symporter (NIS) transports iodide transcellularly from the basolateral to the apical membrane of thyrocyte, where it is organified. The sodium/iodide symporter is also present in non-thyroidal tissues such as the salivary glands, stomach, thymus, and breast [5], so the salivary glands can selectively take up and concentrate iodine [6]. Salivary glands uptake 131I almost 30 to 40 times over its level in plasma; this is sufficient to cause irreversible damage after high doses of 131I [7].

Despite beneficial therapeutic effects, 131I treatment has several side effects, such as xerostomia, xerophtalmia, nausea, vomiting, pain in the neck, tenderness over the parotid and submandibular glands, taste change/loss, sialadenitis, and chronic and recurrent conjunctivitis [8]. The wide spectrum of salivary gland complaints ranges from mild transient discomfort to permanent xerostomia and tooth decay [9]. Major salivary glands (the parotid, submandibular, and sublingual glands) produce 90% of saliva; minor glands produce 10% [10]. Clinicians should be aware of the side effects of 131I on salivary glands, especially when large doses are used [6]. Sialadenitis is the most common complication after 131I ablation therapy. Traditional treatment involves conservative modalities such as aggressive external massage, hydration, steroid treatment, and cholinergic treatment. If there is no response to these conservative treatments, resection of the involved gland is performed [11]. Radioprotective agents can be used for protection of salivary glands from radiation. Many drugs have been assessed for this purpose.

Ours is the first study to evaluate, by histopathological examination, the early radioprotective effect of zinc on the major salivary glands following a high dose of 131I .

Material and Method

After approval from the Local Ethics Committee of Animal Experiments in Ankara Training and Research Hospital, the experiment was conducted in the Husnu Sakal Experimental and Clinical Practice Center.

Sixteen Wistar albino rats with 200-250g body weight and aged 3-5 months were included in the study. The animals were housed under standard laboratory conditions (21±2°C room temperature and 65-70% relative humidity) and fed with standard chow and water ad libitum. Animals were divided into two groups, consisting of eight animals in each group. The first group was the 131I group that was administrated a single dose of 111 MBq (3 mCi) 131I (mon-Iyot 131 Eczacıbaşı/Monrol Nükleer Ürünler Sanayi ve Ticaret Anonim Şirketi Gebze, Kocaeli, Türkiye) by gastric gavage. The second group was the zinc group that was administrated a single dose of 111 MBq (3 mCi) 131I and that was also administered zinc sulphate monohydrate [(10 mg/kg body weight) (Zinco®, Berko, Istanbul, Turkiye)] by gastric gavage. Zinc was started two days before the dose of 131I and was continued for five days after 131I therapy.

Twenty-four hours after the last dosage of zinc, the animals were sacrificed after being anesthetized with 50 mg/kg intraperitoneal propofol (Propofol®, Abbott Laboratory, Istanbul, Turkey). The parotid, submandibular, and sublingual glands were removed bilaterally for histopathological examination.

Pathological Analysis

The lacrimal glands were fixed in 10% neutral buffered formalin (pH 7.2-7.4) for light microscopy and 4-µm-thick paraffin sections were stained with hematoxylin and eosin. The specimens were evaluated using light microscopy (Olympus BX-50, Tokyo, Japan) at 40- to 400-fold magnification in a masked fashion. The slices were evaluated for oedema, vacuolization, panacinar inflammation, necrosis and atrophy in acinar epithelial cells; periductal fibrosis, periductal infiltration, and periductal leakage in interstitial space; duct ectasia and squamous metaplasia in ductal system; and sclerosis and stenosis (fibrin thrombi) in the vascular system.

Results

There were no statistically significant differences in the parotid, submandibular, and sublingual glands between the control and the zinc group in the histopathological evaluation, except for atrophy in the sublingual gland. Atrophy is significantly less seen in the zinc group when compared with the control group in the submandibular gland. But oedema, vacuolization, panacinar inflammation, necrosis, and atrophy in the acinar epithelial cells of the major salivary glands were seen less in the zinc group than in the control group. Periductal fibrosis, periductal inflammation, and periductal leakage were seen less in the zinc group, except for periductal inflammation in the submandibular gland. Ductal ectasia and squamous metaplasia in the ductal system and sclerosis and stenosis (fibrin thrombus) in the vascular system was less than in the zinc group (Table 1-3) (Figure 1-3).

Discussion

The main route of 131I transportation to saliva is the intralobular canal epithelium [12]. 131I is taken up via periductal capillaries, concentrated by ductal epithelium, and secreted to the mouth space through canal lumen [12, 13]. Salivary glands are exposed to ionizing radiation during this process and by adjacent organ uptakes. Damage of the major salivary glands may cause severe reduction in salivary flow and reversible or irreversible impairments in saliva production [14]. Salivary and lacrimal gland dysfunction described as sicca syndrome is relatively frequent after 131I therapy [15]. Stimulation of saliva and radioprotective agents has been studied to prevent these harmful effects on salivary glands. Nakada et al. used lemon candy to decrease salivary gland damage by stimulation of saliva production. In this study, in group 1, lemon candy was started at one hour and in group 2 at 24 hours after 131I therapy. Salivary gland damage decreased in group which lemon candy was given after 24 hours of 131I therapy, but not in control group But they also used steroids, zinc, and vitamin B12 in group 2 differ-

Table 1. Parotid glands of rats. Distribution of histopathological parameters of parotid gland in control and zinc groups with their statistical significance levels.

	Control group (n=8)		Zinc group (n=8)		p
Parotid	Number	Percent	Number	Percent	
Acinar epithelial cells					
Oedema	5	62.5	2	25.0	0.315
Vacuolization	4	50.0	2	25.0	0.608
Panacinar inflammation	3	37.5	1	12.5	0.569
Necrosis	3	37.5	1	12.5	0.569
Atrophy	5	62.5	1	12.5	0.119
Interstitial space					
Periductal fibrosis	3	37.5	2	25.0	1.000
Periductal infiltration	3	37.5	2	25.0	1.000
Periductal leakage	3	37.5	2	25.0	1.000
Ductal system					
Duct ectasia	4	50.0	0	0	0.077
Squamous metaplasia	4	50.0	1	12.5	0.282
Vascular system					
Sclerosis	3	37.5	1	12.5	0.569
Stenosis (fibrin thrombi)	2	25.0	1	12.5	1.000

Table 2. Submandibular glands of rats. Distribution of histopathological parameters of submandibular gland in control and zinc groups with their statistical significance levels.

Submandibular	Control group (n=8)		Zinc group (n=8)		p
	Number	Percent	Number	Percent	
Acinar epithelial cells					
Oedema	3	37.5	2	25.0	1.000
Vacuolization	3	37.5	1	12.5	0.569
Panacinar inflammation	3	37.5	0	0	0.200
Necrosis	3	37.5	1	12.5	0.569
Atrophy	4	50.0	1	12.5	0.282
Interstitial space					
Periductal fibrosis	3	37.5	1	12.5	0.569
Periductal infiltration	2	25.0	2	25.0	1.000
Periductal leakage	4	50.0	2	25.0	0.608
Ductal system					
Duct ectasia	4	50.0	1	12.5	0.282
Squamous metaplasia	3	37.5	2	25.0	1.000
Vascular system					
Sclerosis	3	37.5	1	12.5	0.569
Stenosis (fibrin thrombi)	3	37.5	2	25.0	1.000

ently than in group 1 [16]. Lam and Isselt suggested that the results of the Nakada et al. study are uncertain, as the protective effect may have been due not to the stimulation of saliva production but instead to the aggressive therapy, including zinc, administered to group 2 and that the relationship between the incidence of xerostomia and incidence of symptomatic treatment was uncertain, as reported by Nakada et al. [17]. Silberstein et al. used pilocarpine for the protection of salivary glands and did not find any protective effect of pilocarpine against radiation sialadenitis [18], whereas Aframian et al. reported that pilocarpine may be beneficial in the case of impaired salivary function after 131I treatment [19]. Liu et al. used vitamin C for salivary stimulation. Vitamin C at any time after 131I therapy has only a limited effect on the salivary absorbed dose [20]. Ma et al. reported that amifostine has no significant radioprotective effect on salivary glands. Hydration and acid-stimulating

Table 3. Sublingual glands of rats. Distribution of histopathological parameters of parotid gland in control and zinc groups with their statistical significance levels.

Sublingual	Control group (n=8)		Zinc group (n=8)		p
	Number	Percent	Number	Percent	
Acinar epithelial cells					
Oedema	3	37.5	2	25.0	1.000
Vacuolization	3	37.5	2	25.0	1.000
Panacinar inflammation	4	50.0	0	0	0.077
Necrosis	4	50.0	2	25.0	0.282
Atrophy	5	62.5	0	0	0.026*
Interstitial space					
Periductal fibrosis	4	50.0	2	25.0	0.608
Periductal infiltration	4	50.0	0	0	0.077
Periductal leakage	4	50.0	3	37.5	1.000
Ductal system					
Duct ectasia	3	37.5	1	12.5	0.569
Squamous metaplasia	4	50.0	2	25.0	0.608
Vascular system					
Sclerosis	4	50.0	1	12.5	0.282
Stenosis (fibrin thrombi)	2	25.0	1	12.5	1.000

*Only atrophy is significantly lesser in zinc group

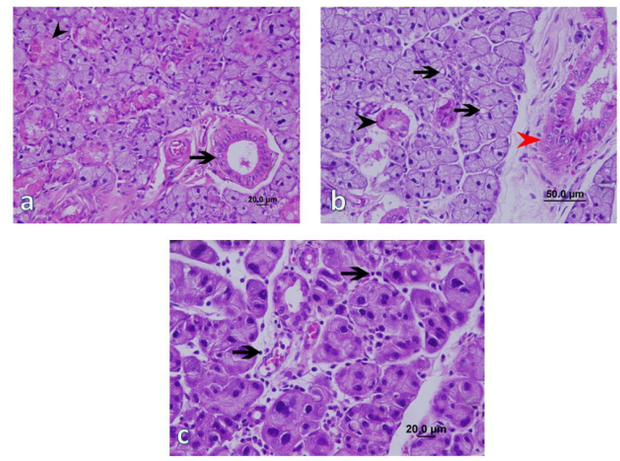

Figure 1. In zinc group, a) Mild ductal ectasia (arrow) and mild necrosis (arrow head), b) Mild vacuolization (arrows), mild ductal atrophy (black arrow head) and mild sclerosis (read arrow head), c) Decrease in the infiltration (arrows).

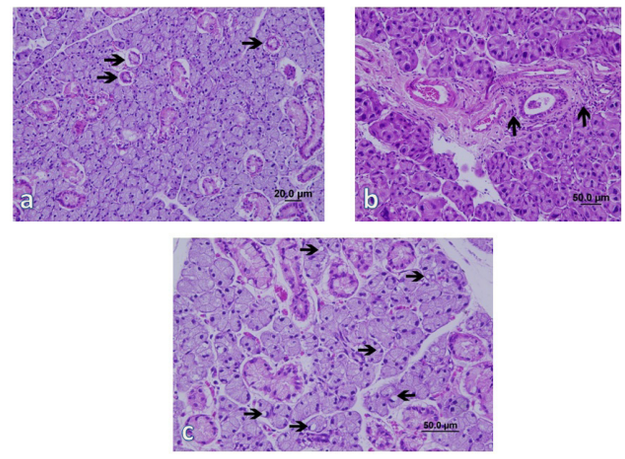

Figure 2. In control group, a) Ductal atrophy (arrows), b) Perivascular and periductal infiltration (arrows), c) Severe vacuolar degeneration (arrows).

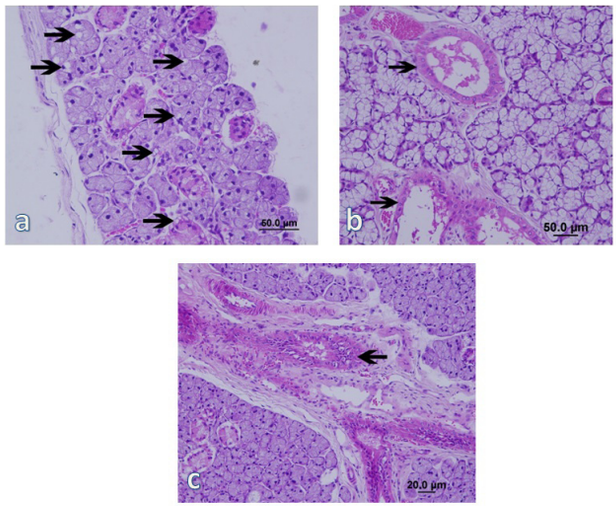

Figure 3. In control group, a) Severe vacuolization (arrows), b) Ductal ectasia (arrows), c) Vascular sclerosis (arrows).

agents should be the first choices during 131I treatment [21]. Crescenti et al. used a combination consisting of Se, Zn, and Mn plus Lachesis muta venom on the rats. All animals of the untreated group died after whole body irradiation with 8 and 10 Gy while most of the rats in the treated group survived. This combination also prevented radiation-induced loss of salivary gland function and morphological alterations [22].

Salts of zinc have been found to be radioprotective on plants in the zone of Chernobyl nuclear power station as they decreased the uptake of 90Sr and 137Cs through the roots [23]. Zinc aspartate protected mice from the lethal effects of radiation and raised the LD50 from 8 Gy to 12.2 Gy, but zinc sulphate and zinc chloride were less active when compared with zinc aspartate [24]. In our study we used zinc sulphate and this may have caused the limited radioprotective effect on the salivary glands. In another study, zinc salts reduced the fall of hematocrit, thrombocytes, erythrocytes, and leucocyte levels in irradiated mice [25]. Zinc was used in combination with other protective agents. The use of combinations of radioprotective agents is effective for maximal radioprotection with minimal adverse effects, because combining reduces the dose of each compound and the toxicities that can limit their usefulness [26]. Combined doses of zinc aspartate and WR 2721 have protective effect against radiation lethality and radiation-induced lymphoid tumors whereas each agent when used separately displayed no effect [27]. Zinc aspartate is better tolerated and has a more favourable therapeutic index than aminothiol radioprotectors [28].

Ogata and Izumo observed the radioprotective effect of a subcutaneous single dose of inorganic zinc 24 hours before gamma ray irradiation with a sublethal dose [29].

As a conclusion, this is the first study about the radioprotective effect of zinc in the early histopathological effects of 131I therapy. Because of the small study groups, results were not statistically significant, but almost all of the histopathological parameters were seen less in the zinc treated group in all major glands, except for periductal inflammation in the submandibular gland. Large animal groups should be studied for better statistical analysis.

Competing interests

The authors declare that they have no competing interests.

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